# EXHIBIT A

## SUMMARY OF PRODUCT CHARACTERISTICS

## 1 Trade name of the medicinal product

Albumin Octapharma 50 mg/ml solution for infusion

## 2 Qualitative and quantitative composition

**Active ingredients**

Human albumin

The solution contains 50 mg/ml of protein of which at least 96% is human albumin.

Each 100 ml contains 5 g of human albumin.

Albumin 50 mg/ml is a mildly hypooncotic solution.

For excipients, see section 6.1.

## 3 Pharmaceutical form

Solution for infusion.

Clear or slightly opalescent.

## 4 Clinical particulars

### 4.1 Therapeutic indications

Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate.
The choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient, based on official recommendations.

### 4.2 Posology and method of administration

The concentration of the albumin preparation, dosage and the infusion-rate should be adjusted to the patient´s individual requirements.

Posology

The dose required depends on the size of the patient, the severity of trauma or illness and on continuing fluid and protein losses. Measures of adequacy of circulating volume and not plasma albumin levels should be used to determine the dose required.

If human albumin is to be administered, haemodynamic performance should be monitored regularly; this may include:

- arterial blood pressure and pulse rate
- central venous pressure
- pulmonary artery wedge pressure
- urine output
- electrolyte
- haematocrit/haemoglobin

This product is suitable for premature infants and dialysis patients.

Method of administration

Human albumin can be directly administered by the intravenous route.

The infusion rate should be adjusted according to the individual circumstances and the indication.

In plasma exchange the infusion rate may be higher and should be adjusted to the rate of removal.

## 4.3 Contraindications

Hypersensitivity to albumin preparations or to any of the excipients.

## 4.4 Special warnings and special precautions for use

If allergic or anaphylactic-type reactions occur, the infusion should be stopped immediately and appropriate treatment instituted. In case of shock, the current medical standards for shock-treatment should be observed.

Albumin should be used with caution in conditions where hypervolaemia and its consequences or haemodilution could represent a special risk for the patient. Examples of such conditions are:

- Decompensated cardiac insufficiency
- Hypertension
- Oesophageal varices
- Pulmonary oedema
- Haemorrhagic diathesis
- Severe anaemia
- Renal and post-renal anuria

20-25% Human albumin solutions are relatively low in electrolytes compared to the 4-5% human albumin solutions. When albumin is given, the electrolyte status of the patient should be monitored (see 4.2) and appropriate steps taken to restore or maintain the electrolyte balance.

Albumin solutions must not be diluted with water for injections as this may cause haemolysis in recipients.

If comparatively large volumes are to be replaced, controls of coagulation and haematocrit are necessary. Care must be taken to ensure adequate substitution of other blood constituents (coagulation factors, electrolytes, platelets and erythrocytes).

Hypervolaemia may occur if the dosage and rate of infusion are not adjusted to the patients circulatory situation. At the first clinical signs of cardiovascular overload (headache, dyspnoea, jugular vein congestion), or increased blood pressure, raised venous pressure and pulmonary oedema, the infusion is to be stopped immediately.

Standard measure to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

There are no reports of virus transmissions with albumin manufactured to European Pharmacopeia specifications by established processes.

It is strongly recommended that every time that Albumin Octapharma is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

## 4.5 Interactions with other medicinal products and other forms of interactions

No specific interactions of human albumin with other medicinal products are known.

## 4.6 Pregnancy and lactation

The safety of Albumin Octapharma for use in human pregnancy has not been established in controlled clinical trials. However, clinical experience with albumin suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

No animal reproduction studies have been conducted with Albumin Octapharma. However, human albumin is a normal constituent of human blood.

## 4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

## 4.8 Undesirable effects

Adverse reactions for Albumin Octapharma are rare. These reactions normally disappear rapidly when the infusion rate is slowed down or the infusion is stopped. In case of severe reactions, the infusion should be stopped and an appropriate treatment should be initiated.

The following adverse reactions have been observed for Albumin Octapharma during the postmarketing phase.

Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

| System Organ Class | Rare | Very rare |
|---|---|---|
| | | |
| *Immune system disorders* | anaphylactic reaction | anaphylactic shock |
| | | |
| *Psychiatric disorders* | | confusional state |
| | | |
| *Nervous system disorders* | | headache |
| | | |
| *Cardiac disorders* | | tachycardia<br>bradycardia |
| | | |
| *Vascular disorders* | hypotension | hypertension<br>flushing |
| | | |
| *Respiratory, thoracic and mediastinal disorders* | | dyspnoea |
| | | |
| *Gastrointestinal disorders* | | nausea |
| | | |
| *Skin and subcutaneous tissue disorders* | | urticaria<br>angioneurotic oedema<br>rash erythematosus<br>increased sweating |
| | | |
| *General disorders and administration site conditions* | | fever<br>rigors |

For information on viral safety see 4.4.

## 4.9 Overdose

Hypervolaemia may occur if the dosage and rate of infusion are too high. At the first clinical signs of cardiovascular overload (headache, dyspnoea, jugular vein congestion), or increased blood pressure, raised central venous pressure and pulmonary oedema, the infusion should be stopped immediately and the patient's haemodynamic parameters carefully monitored.

## 5 Pharmacological properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: plasma substitutes and plasma protein fractions, ATC code: B05A A01

Human albumin accounts quantitatively for more than half of the total protein in the plasma and represents about 10% of the protein synthesis activity of the liver.

Physiochemical data:
Human albumin 50 mg/ml is mildly hypooncotic to normal plasma.

The most important physiological function of albumin results from its contribution to oncotic pressure of the blood and transport function. Albumin stabilises circulating blood volume and is a carrier of hormones, enzymes, medicinal products and toxins.

### 5.2 Pharmacokinetic properties

Under normal conditions the total exchangeable albumin pool is 4-5 g/kg body weight of which 40-45% is present intravascularly and 55-60% in the extravascular space. Increased capillary permeability will alter albumin kinetics and abnormal distribution may occur in conditions such as severe burns or septic shock.

Under normal conditions, the average half-life of albumin is about 19 days. The balance between synthesis and breakdown is normally achieved by feed-back regulation. Elimination is predominantly intracellular and due to lysosome proteases.

In healthy subjects, less than 10% of infused albumin leaves the intravascular compartment during the first 2 hours following infusion. There is considerable individual variation in the effect on plasma volume. In some patients the plasma volume can remain increased for some hours. However, in critically ill patients, albumin can leak out of the vascular space in substantial amounts at an unpredictable rate.

### 5.3 Preclinical safety data

Human albumin is a normal constituent of human plasma and acts like physiological albumin.

In animals, single dose toxicity testing is of little relevance and does not permit the evaluation of toxic or lethal doses or of a dose-effect-relationship. Repeated dose

toxicity testing is impracticable due to the development of antibodies to heterologous protein in animal models.

To date, human albumin has not been reported to be associated with embryo-foetal toxicity, oncogenic or mutagenic potential.

No signs of acute toxicity have been described in animal models.

## 6 Pharmaceutical particulars

### 6.1 List of excipients

N-acetyl-DL-tryptophan

Caprylic acid

Water for injections

*Electrolytes*

| | | |
|---|---|---|
| Sodium | 142.5-157.5 | mmol/l |
| Potassium | max. 1.0 | mmol/l |

### 6.2 Incompatibilities

Human albumin solution must not be mixed with other medicinal products, whole blood and packed red cells.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Do not store and transport above 25 °C.

Store in the original container in order to protect from light.

Do not freeze.

### 6.5 Nature and contents of container

- 100 ml of solution in infusion bottle (type II glass) with stopper (bromobutyl rubber). Pack of 1.
- 250 ml of solution in infusion bottle (type II glass) with stopper (bromobutyl rubber). Pack of 1.

### 6.6 Instructions for use and handling and disposal

The solution can be directly administered by the intravenous route.

Albumin solutions must not be diluted with water for injections as this may cause haemolysis in recipients.

If large volumes are administered, the product should be warmed to room or body temperature before use.

The solution should be clear or slightly opalescent. Do not use solutions which are cloudy or have deposits. This may indicate that the protein is unstable or that the solution has become contaminated.

Once the infusion container has been opened the content should be used immediately.

Any unused product should be disposed of in accordance with local requirements.

## 7 Marketing authorisation holder

Octapharma AB
112 75 Stockholm

## 8 Marketing authorisation number

13521

## 9 Date of first authorisation/ renewal of the authorisation

1999-11-04/2004-11-04

## 10 Date of revision of the text

2005-03-04